

Day and Night Home Closed-Loop Insulin Delivery in Adults with Type 1 Diabetes: Three Centre Randomised Crossover Study

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ABSTRACT

Objective

To evaluate the feasibility of day and night closed-loop insulin delivery in adults with type 1 diabetes under free-living conditions.

Methods

Seventeen adults with type 1 diabetes on insulin pump therapy [age 34 ± 9 years; HbA1c $7.6\pm 0.8\%$; duration of diabetes 19 ± 9 years; mean \pm SD] participated in an open-label multinational three-centre cross-over study. In a random order participants underwent two eight day periods (first day at the clinical research facility followed by seven days at home) of sensor augmented insulin pump therapy or automated closed-loop insulin delivery. The primary endpoint was the time when sensor glucose was in target range between 3.9 and 10.0 mmol/l during the seven day home phase.

Results

During the home phase, the percentage time when glucose was in target range was significantly higher during closed-loop compared to sensor augmented pump therapy (75 [61, 79] vs. 62 [53, 70]%, median [IQR], $p=0.005$). Mean glucose (8.1 vs. 8.8 mmol/l, $p=0.027$) and time spent above target ($p=0.013$) were lower during closed-loop while time spent below target was comparable ($p=0.339$). Increased time in target was observed during both day-time ($p=0.017$) and night-time ($p=0.013$).

Conclusions

Compared to sensor augmented pump therapy, one week closed-loop insulin delivery at home reduces mean glucose and increases time in target without increasing the risk of hypoglycaemia in relatively well controlled adults with type 1 diabetes.

Keywords: type 1 diabetes, closed-loop insulin delivery, model predictive control, continuous subcutaneous insulin infusion, continuous glucose monitoring, artificial pancreas

Despite significant improvements in the care of type 1 diabetes, achieving good glycaemic control while avoiding hypoglycaemia (1) remains a challenge for many patients (2; 3). Insulin pump therapy and real time continuous glucose monitoring (CGM) have shown to improve HbA1c (4; 5) and reduce hypoglycaemia (6; 7) particularly when using low glucose suspend (8; 9). Closed-loop insulin delivery is an emerging treatment option combining these technological advances (10) to modulate delivery of insulin in a glucose responsive fashion. Closed-loop differs from conventional pump therapy, characterised by pre-programmed basal delivery, through the use of a control algorithm which directs subcutaneous insulin delivery according to sensor glucose levels. Several studies have evaluated the safety and efficacy of closed-loop under laboratory conditions and shown promising results. These include evaluations using a randomised design by our group in youths (11; 12), adults (13), and pregnant women (14) and by others using the model predictive control algorithm (15; 16), the proportional-integral-derivative approach (17; 18), and the fuzzy logic controller (19; 20). Insulin and glucagon co-administration have also been applied in studies (21-23).

In contrast to studies conducted in the clinical research facility with carefully controlled conditions, closed-loop at home is exposed to considerably more varied meal and exercise patterns. Participants may over- or underestimate carbohydrate content and may undertake unplanned activity and/or exercise. Patients using insulin pump therapy are advised to use temporary reductions or increments of basal insulin delivery to meet these demands but this requires a degree of planning and user intuition and interaction. Since closed-loop systems modulate delivery of insulin in a glucose responsive fashion (10), it may be able to achieve better glucose control than pre-programmed basal rates of conventional pump therapy.

In February 2010, the European Union granted funding to the AP@home consortium of European academic medical centres, biotechnology companies and industrial partners to carry out closed-loop glucose control research (24). The first major closed-loop study performed by the AP@home consortium evaluated the feasibility of day and night closed-loop insulin delivery using two different algorithms in 47 adults with type 1 diabetes (25). The present study was undertaken to evaluate the performance of day and night closed-loop insulin delivery with Cambridge algorithm over seven days at home preceded by one day control at the clinical research facility.

METHODS

Participants and study design

The study adopted an open-label prospective multinational three-centre randomised cross-over design. The study protocol was approved by respective research ethics committees and regulatory authorities in the UK, Germany and Austria. Study participants were recruited between January 2013 and August 2013 through adult diabetes clinics and other established methods at each participating centre (Addenbrooke's Hospital, Cambridge, UK; Profil Institute, Neuss, Germany; and Medical University of Graz, Graz, Austria). Key inclusion criteria were age ≥ 18 years, diagnosis of type 1 diabetes, treatment with insulin pump therapy for at least 3 months, willingness to perform at least six finger-stick glucose measurements per day, and HbA1c $\leq 10\%$ (86 mmol/mol). Key exclusion criteria were concurrent illness or medications likely to interfere with interpretation of study results, recurrent severe hypoglycaemia, significant hypoglycaemia unawareness, total daily insulin dose ≥ 2.0 U/kg, clinically significant nephropathy, neuropathy, or retinopathy, severe visual or hearing impairment, pregnancy and breast feeding. All participants provided written informed consent prior to study related activities.

Study procedures:

After enrolment, participants were trained on the use of study insulin pump (Dana R Diabecare, Sooil, Seoul, South Korea) and continuous glucose monitoring device (FreeStyle Navigator, Abbott Diabetes Care, Alameda, CA, USA) (26). The study insulin pump was programmed with participant's usual basal settings as well as usual insulin to carbohydrate ratios and correction factors. Participants were advised

to use the bolus calculator for all meals during the entire study period. Ability to use study devices was formally assessed using competency assessment and additional training was provided as required. After a run-in period of seven days to three weeks, participants underwent two eight day periods; in random order, when glucose was controlled either by sensor augmented insulin pump therapy (SAP) or closed-loop insulin delivery. The first day of each study period was conducted at a clinical research facility. After the first day, participants continued study interventions for the next seven days under free-living conditions in their home and work environment. The two intervention periods were separated by a one to four week washout. No changes were made to usual treatment parameters. Participants were advised to calibrate the CGM device according to manufacturer's instructions (26) and use the built-in glucometer for all finger-stick measurements and to keep a diary for detailed documentation.

Inpatient stay

At the start of each study intervention, participants were admitted to the clinical research facility around 07:30 hours. On arrival, an intravenous cannula was inserted to allow for frequent venous sampling starting at 08:30 hours. Venous blood samples were collected at 30 minute intervals for the measurement of plasma glucose between 08:30 and 23:00 hours followed by every 60 minutes thereafter till 07:00 hours the following morning. Closed-loop and SAP treatment commenced at 09:00 hours with breakfast.

Participants consumed standardized meals; breakfast 50 g, lunch 60 g and dinner 80 g of carbohydrates; at 09:00, 13:00 and 20:00 hours. Fifteen minutes

before each meal an insulin bolus was delivered, calculated according to usual settings and pre-meal finger-stick glucose levels. The insulin bolus was given with the meal if finger-stick glucose was ≤ 4.0 mmol/l. Meal content and bolus procedure of each study intervention was identical. Participants consumed optional snacks containing 20g carbohydrate at 16:00 hours and 15g carbohydrate at 22:00 hours. During the closed-loop visit, no insulin bolus was given for snacks but during the SAP visit participants received pre-snack bolus as per usual practice. Rapid-acting insulin analogue aspart (Novo Nordisk, Bagsvaerd, Denmark) was used throughout the study. During the closed-loop visit, participants received additional training on starting, stopping, and safe operation of the closed-loop system. Competency on the use of closed-loop system was assessed by the study team prior to discharge.

Home phase

Seven day home phase commenced at the end of the one day inpatient stay. Participants were provided with a custom made pouch to carry the small portable computer running the algorithm and CGM device (Supplemental Online Material, Figure S1). As a precaution, participants were advised not to drive or undertake strenuous physical exercise while the closed-loop system was in operation but were encouraged to engage in usual daily activities including going to work and moderate activity such as walking and daily housework. Participants were provided with a 24-hour telephone helpline and were advised to follow usual treatment guidelines during inter-current illness, hyperglycaemia and hypoglycaemia. They were free to consume meals of choice including eating out. During closed-loop intervention, participants were not required to give insulin bolus for snacks below 30 g of carbohydrate and

during both study interventions participants were free to decide on alarm thresholds for the CGM device.

Closed-loop system

The Florence closed-loop system (University of Cambridge, Cambridge, UK) (27) comprises a model predictive control algorithm residing on an ultraportable laptop (OQO Model 02 computer, OQO, CA, USA), which is linked to the CGM receiver by a USB cable and controls the study pump over wireless communication. Every 12 minutes, the algorithm calculated a new insulin infusion rate which was automatically sent to the study insulin pump. The calculations utilised a compartment model of glucose kinetics (28) describing the effect of rapid-acting insulin analogues and the carbohydrate content of meals on glucose levels. Participants were required to count the carbohydrates and use the pump bolus calculator for pre-meal boluses as per usual practice. Meal bolus also included a correction bolus as calculated by the bolus wizard if the glucose was outside target range.

Carbohydrate content of consumed meals and insulin delivery history including manually instructed bolus, were downloaded automatically from the study pump. The algorithm was initialized using pre-programmed basal insulin delivery downloaded from the study pump. Additionally, participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to a particular participant. The treat-to-target control algorithm aimed to achieve glucose levels between 5.8 and 7.3 mmol/l and adjusted the actual level depending on fasting vs. postprandial status and the accuracy of model-based glucose predictions. A sample 24 hour section of closed-loop study arm is shown in

Supplemental Online Material Figure S2 and interface of the closed-loop system is shown in Supplemental Online Material Figure S3. Algorithm version 0.3.24 with interface version 1.0.7 was used (University of Cambridge, Cambridge, UK).

Safety precautions during closed-loop

Participants were trained to perform calibration check before breakfast and evening meal. If sensor glucose was above finger-stick glucose by more than 3 mmol/l, the CGM was re-calibrated. There was no re-calibration for sensor under reading. These instructions resulted from an *in silico* evaluation of hypoglycaemia and hyperglycaemia risk (29) using the validated Cambridge simulator (30).

If sensor glucose became unavailable, pre-programmed insulin delivery was automatically restarted within 30 minutes or within 1 hour in case of other failures. This limited the risk of insulin under- and over-delivery (29). Safety rules limited maximum insulin infusion and suspended insulin delivery at sensor glucose at or <4.3mmol/l or when sensor glucose was rapidly decreasing.

Assays

During the in-patient stay, a YSI2300 STAT Plus Analyzer (YSI, Lynchford House, Farnborough, UK; intra-assay coefficient of variation (CV) 1.5% and inter-assay CV 2.8%) was used for determination of plasma glucose.

Statistical analysis

The analysis plan was agreed in advance. All analyses were undertaken on intention to treat basis. The primary outcome was the time when glucose was in the target range 3.9 to 10.0 mmol/l during the home study phase. Secondary outcomes were mean glucose, time when glucose was <3.9 mmol/l and <2.8 mmol/l (hypoglycaemia), time when glucose was >10.0 mmol/l and >16.7 mmol/l (hyperglycaemia), low and high blood glucose index and insulin delivery. We estimated glycaemic variability by the standard deviation of glucose and the coefficient of variation. The low and high blood glucose index assessing the duration and extent of hypo- and hyperglycaemia was calculated as an average of transformed glucose measurements progressively increasing at low and high glucose levels (31). We corrected for bias resulting from simultaneous use of sensor glucose to direct insulin delivery and to assess outcomes by using adjusted glucose - a stochastic transformation of glucose metrics when assessing time glucose was in, below, and above target range (32). Other glucose metrics such as mean glucose and glucose variability were calculated utilising native (unadjusted) sensor glucose levels.

Secondary outcomes were calculated for the one day inpatient stay, seven day home phase as a whole and daytime (07:00 till 23:00 hours) and overnight (23:00 till 07:00 hours) periods. During the inpatient stay, study outcomes were calculated using both YSI laboratory glucose measurements and sensor glucose. Calculations were made using GStat software, Version 2.0 (University of Cambridge). Statistical analyses were conducted with the use of SPSS, Version 19 (IBM Software, Hampshire, UK). Normally distributed data were compared using paired t-test while non-normally distributed data were compared using Wilcoxon signed rank test. Values are reported as mean \pm SD or median (interquartile range: quartile 1 to quartile 3) unless stated

otherwise. All p-values are two-tailed and values less than 0.05 were considered statistically significant.

RESULTS

From January 2013 to August 2013, 24 volunteers were screened and 21 enrolled. Four dropouts were recorded, two during the first study period, one during the run-in phase, and another during the washout period leaving 17 completed participants [age 34 ± 9 years; HbA1c $7.6\pm 0.8\%$; duration of diabetes 19 ± 9 years; duration of pump therapy 5.6 ± 6.9 years; Supplemental Online Material Table S1].

Glucose control and insulin delivery during the home phase

The primary study outcome, the adjusted time spent in target glucose range 3.9 to 10.0 mmol/l at home, was higher during closed-loop insulin delivery (74.5 [61.1, 78.9] vs. 61.8 [53.3, 70.1]%, $p=0.005$, Table 1). Closed-loop reduced mean glucose (8.1 ± 1.0 vs. 8.8 ± 1.0 mmol/l, $p=0.027$) and the adjusted time spent above target glucose level (21.9 [16.7, 32.3] vs. 30.5 [24.3, 41.4] %, $p=0.013$), without increasing the time spent in hypoglycaemia. Measured as the standard deviation, variability of glucose was lower during closed-loop (2.9 ± 0.6 vs. 3.3 ± 0.8 , $p=0.034$) but no difference was observed using the coefficient of variation (35.7 ± 5.9 vs. 37.7 ± 7.6 , $p=0.149$). Sensor glucose profiles during the two treatments periods are shown in Figure 1 with particularly pronounced difference during the overnight period. Fourteen participants (82%) showed increased time in target during closed-loop compared to SAP (Figure 2). Native sensor glucose levels (Supplemental Online Material Table S2) concurred with the assessment by adjusted values (Table 1).

As expected, variability of basal insulin delivery was significantly higher during closed-loop (Table 2). Bolus and basal insulin infused during day was significantly different between the two interventions; during closed-loop period lower bolus

amount and higher basal dose were observed. Overall there was tendency towards lower total daily dose during closed-loop but this did not reach statistical significance ($p=0.109$).

Day and night glucose control during the home phase

Closed-loop increased time in target during both day-time (target 3.9 to 10.0 mmol, 72.5% vs. 65.4%, $p=0.017$) and night-time (target 3.9 to 8.0 mmol/l, 48.4% vs. 35.1%, $p=0.013$) (Table 2). In addition, mean sensor glucose was lower during night-time period (8.3 ± 1.3 vs. 9.3 ± 1.1 , $p=0.015$). There was no difference in the area under the curve for hypoglycaemia during either period (Table 2).

Glucose control and insulin delivery during the one day inpatient stay

Time spent in target glucose range 3.9 to 10.0 mmol/l was higher with closed-loop during the inpatient stay (YSI based results Table 1 and CGM based results Supplemental Online Material Table S3). The number of rescue carbohydrate treatments required was lower during closed-loop (closed-loop 7 vs. SAP 16) but did not reach statistical significance ($p=0.215$). Closed-loop administered significantly lower total insulin daily dose during the inpatient stay (36.8 vs. 41.8 U, $p=0.028$).

Sensor accuracy during inpatient stay

Sensor performance was good with median absolute deviation of 0.8 (0.4, 1.3) mmol/l and median absolute relative deviation (MARD) of 10.0% (4.7, 16.3). Detailed

clinical and numerical sensor accuracy is shown in Supplemental Online Material Table S4. Eighty three percent of YSI-sensor pairs were in Clarke Error Grid Zone A.

Adverse events

Two severe hypoglycaemic events occurred during the study; one event during closed-loop arm and one event during washout period. The severe hypoglycaemia event during the closed-loop period occurred at a time when closed-loop was non-operational due to sensor unavailability and insulin was being delivered according to participant's usual pump settings. The second severe hypoglycaemia episode leading to hospital admission occurred during washout while the participant was using usual pump treatment in the context of inter-current illness. Both participants fully recovered with no clinical sequela. Both episodes most likely resulted from over aggressive manual insulin bolus corrections. Four episodes of high glucose occurred due to infusion set failure (no significant ketosis). One participant suffered from a transient vasovagal episode during the one day in-patient stay and fully recovered with intravenous fluid treatment.

Utility analysis

During the one day inpatient stay closed-loop was operational 98.4 [95.8, 100] % of time. During home phase closed-loop operational time was 83.0 [71.1, 92.3] %. Availability of CGM during home phase was 95.0 [85.2, 97.8] % during closed-loop and 95.1 [92.6, 97.4] % during SAP. Closed-loop operational time when CGM data were available was 90.9 [83.7, 96.2] %.

Reasons for not using closed-loop during home phase included unavailability of CGM data, periods of driving and strenuous exercise, non-operational laptop, and unreliable Bluetooth communication between pump and the computer. Detailed analysis of failure events is shown in Supplemental Online Material Table S5. The most common reason for undesired cessation of closed loop was failure of Bluetooth pump communication. In total there were 91 instances of pump communication failures giving a mean interval between failures of 25.6 hours. Out of the 91 instances 47 instances were recorded in 3 participants. Excluding these 3 participants the mean interval between pump communication failures was 53 hours.

CONCLUSIONS

The present study demonstrates the feasibility of unsupervised day and night closed-loop insulin delivery under free-living conditions in adults with type 1 diabetes. When applied in a relatively well controlled cohort, compared to current best therapy, closed-loop increased the time when glucose was in the target range while reducing the mean glucose. Importantly, these improvements were achieved without increasing the risk of hypoglycaemia while administering similar amount of total daily insulin dose. Benefits of closed-loop were more pronounced during the overnight period although glucose control was superior during both day and night time. Other benefits include reduced glucose variability as measured by standard deviation and reduced high glucose excursions. In agreement with results obtained during the seven day home phase, participants also showed improved plasma glucose control with closed-loop during the one day stay at the clinical research facility while infusing a significantly lower amount of insulin.

In the current study there was no statistically significant decrease in the time spent in hypoglycaemia. This can be explained by the study not being powered to detect such a difference although trend towards a lower hypoglycaemia exposure was observed (AUC below 3.5 mmol/l 71% lower during closed-loop; 2.9% vs 7.9%, CL vs SAP; $p=0.14$). Low levels of hypoglycaemia were observed compared to, for example, Juvenile Diabetes Research Foundation CGM trial (5) which recorded time spent in hypoglycaemia (< 3.9 mmol) of 89 and 60 minutes per day prior and after the use of real time CGM. Participants in the present study spent 40 and 49 minutes per day during closed loop and control periods; excluding subjects with significant co-

morbidities and hypoglycaemia unawareness may have led to selection of participants with a lower hypoglycaemia risk.

A smart phone based closed-loop control platform was previously evaluated in 20 adults in four clinical centres in a non-randomised single arm study design in a home like environment (hotel / guest house or mixed hospital-hotel admissions) (33). The study duration was 42 hours with first 14 hours of operation under open loop control followed by 28 hours of closed-loop. In contrast, out-patient closed-loop duration in the present study was longer at 168 hours per participant. Two further randomised crossover studies have evaluated the use of overnight closed-loop outside clinical research facility. The first study showed reduced rates of hypoglycaemia during a single night at three youth diabetes camps (34). An interim analysis from the second study using closed-loop at home for four nights have also shown reduced hypoglycaemia burden (35). Feasibility of dual hormone closed-loop under free living conditions at home for 48 hours have been evaluated but despite the use of glucagon this study reported more hypoglycaemia during closed-loop arm (36).

During the present proof-of-concept study, a prototype closed-loop system was used with the objective to assess the feasibility of day and night hybrid closed-loop. Participants were required to carry the ultra-portable computer in a removable pouch. When CGM was available closed-loop was operational over 90% of time during the home phase. Based on encouraging results from the current study, a closed-loop system based on smart phone technology suitable for longer studies is under development. During current study, there was no dedicated treatment optimisation period and participants were only informed about insulin requirements in

each study period after completion of the study minimising any influence arising from the cross over study design.

Training on closed-loop system took about 60 minutes. Closed-loop technology appears simple to initiate once insulin pump therapy and continuous glucose monitoring is established. A more comprehensive training was administered at study start, to familiarise participants with the study pump and continuous glucose monitoring. The two severe hypoglycaemic events seen during current study were unrelated to closed-loop insulin delivery.

The strengths of our study are the integration of closed-loop into normal life including use at work, weekends, holidays, varied diet and sleeping patterns and randomised crossover study design in multinational multicentre settings. Participants started and stopped closed-loop without supervision.. Weaknesses include a small sample size, an early generation closed-loop system (which is not a commercially available product), and a relatively short study duration.

In conclusion, day and night closed-loop can be used safely at home and its benefits include increased time when glucose is in target and reduced mean glucose. Larger and longer studies are warranted.

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Author contributions: RH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LL, RH and CB coordinated the study. LL, SD, JKM, MEW, ME, LH, TRP, SA, MLE and RH co-designed the study. LL, HT, JKM, SD, LM, were responsible for screening and enrolment of participants and arranged informed consent from the participants. LL, HT, SD, JKM, WD, LM, HK, JAM, and SH, provided patient care and/or took samples. LL, MEW, WD and LM carried out randomization. MN and LL carried out the data analysis, including the statistical analyses. RH designed and implemented the glucose controller. RH, LL, MLE, LH, TRP, SA, ME contributed to the interpretation of the results. LL and RH wrote the manuscript. All authors critically reviewed the report. No writing assistance was provided.

Conflict of interest disclosures: RH reports having received speaker honoraria from Minimed Medtronic, Lifescan, Eli Lilly, BBraun, and Novo Nordisk, serving on advisory panel for Animas, Minimed Medtronic, and Eli Lilly, receiving license fees from BBraun and Beckton Dickinson; and having served as a consultant to Beckton Dickinson, BBraun, Sanofi, and Profil. MLE reports having received speaker honoraria from Abbott Diabetes Care, Animas, serving on advisory board for Medtronic, Roche, Cellnovo. MEW has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. RH and MEW report patent applications. LH is partner and consultant of Profil Institut für Stoffwechselforschung, Neuss, Germany and Profil Institute for Clinical Research, San Diego, USA. He is a consultant for a number of companies that are developing novel diagnostic and therapeutic options. JKM reports having received speaker honoraria from

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Table 1: Glucose control during closed-loop and sensor augmented pump therapy over the seven day home phase and one-day stay at the clinical research facility in 17 patients with type 1 diabetes.

	<i>Closed-loop</i>	<i>SAP</i>	<i>P</i> *
Free living conditions (7 days) - based on CGM			
Mean glucose (mmol/l)**	8.1 ± 1.0	8.8 ± 1.0	0.027
SD of glucose (mmol/l)**	2.9 ± 0.6	3.3 ± 0.8	0.034
CV of glucose (%) **	35.7 ± 5.9	37.7 ± 7.6	0.149
Time spent at glucose level (%)			
3.9 to 10.0 mmol/l [‡]	74.5 (61.1, 78.9)	61.8 (53.3, 70.1)	0.005
3.9 to 10.0 mmol/l**	75.3 (62.1, 82.0)	62.6 (54.8, 72.4)	0.006
3.9 to 8.0 mmol/l [‡]	54.9 (42.2, 58.3)	43.3 (33.0, 49.1)	0.017
>10.0 mmol/l [‡]	21.9 (16.7, 32.3)	30.5 (24.3, 41.4)	0.013
>16.7 mmol/l [‡]	1.5 (0.5, 3.5)	3.3 (1.4, 5.0)	0.049
<3.9 mmol/l [‡]	3.7 (2.2, 7.9)	5.0 (2.3, 8.5)	0.339
<2.8 mmol/l [‡]	0.3 (0.2, 1.1)	0.6 (0.2, 1.6)	0.124
AUC _{DAY} <3.5 mmol/l** (mmol/l × minutes)	2.9 (1.4, 15.8)	7.9 (1.3, 24.1)	0.149
LBGI**	0.6 (0.5, 1.4)	0.9 (0.5, 1.5)	0.309
HBGI**	4.5 (3.3, 7.2)	7.2(4.8, 9.1)	0.039
Clinical research facility (one day) - based on YSI glucose			
Mean glucose (mmol/l)	8.2 ± 1.0	8.6 ± 1.6	0.292
SD of glucose (mmol/l)	2.4 ± 0.7	2.8 ± 0.7	0.079
CV of glucose (%)	27.5 ± 8.3	33.0 ± 8.4	0.095
Time spent at glucose level (%)			
3.9 to 10.0 mmol/l	73.7 (63.4, 84.1)	60.7 (49.2, 76.8)	0.044
<3.9 mmol/l	1.8 (0, 5.8)	4.7 (0, 7.8)	0.221
>10.0 mmol/l	21.4 (13.6, 33.5)	24.5 (16.0, 49.1)	0.124

Data shown are mean ± SD or median (IQR), *Paired samples t-test or Wilcoxon signed Rank Test.

** Based on native CGM, [‡] Adjusted for CGM measurement error assuming a relative absolute deviation of 15%, ** Based on native CGM

SAP= sensor augmented pump therapy; LBGI and HBGI=low and high blood glucose index; CGM=continuous glucose monitoring, AUC – area under the curve calculated per day

Table 2: Insulin delivery and day-time and night-time glucose control during the home phase.

	<i>Closed loop</i>	<i>SAP</i>	<i>P</i> *
Insulin delivery			
Total basal (U) / day	20.1 (17.2, 24.7)	18.9 (15.4, 20.4)	0.017
Total bolus (U) / day	18.9 (15.5, 25.5)	26.5 (20.6, 30.1)	0.002
Total daily dose (U)	39.1 (34.7, 45.7)	44.7 (36.3, 51.0)	0.109
SD of basal insulin	0.7 (0.6, 0.9)	0.2 (0.1, 0.2)	<0.001
Day-time and night-time glucose control			
Day-time (07:00 till 22:59 hours)			
Mean glucose	8.1 ±1.0	8.5 ± 1.2	0.147
Time in target (3.9 to 10 mmol/l) [‡]	72.5 (63.4, 78.6)	65.4 (54.6, 71.0)	0.017
AUC _{DAY} below 3.5 mmol/l (mmol/l × minutes)	2.3 (0.9, 19.3)	6.3(0.4, 30.1)	0.225
Night-time (23:00 till 06:59 hours)			
Mean glucose	8.3 ± 1.3	9.3 ± 1.1	0.015
Time in target (3.9 to 8 mmol/l) [‡]	48.4 (32.5, 64.5)	35.1 (28.4, 47.5)	0.013
AUC _{DAY} below 3.5 mmol/l (mmol/l × minutes)	3.1 (0, 17.5)	3.2 (0.1, 33.5)	0.163

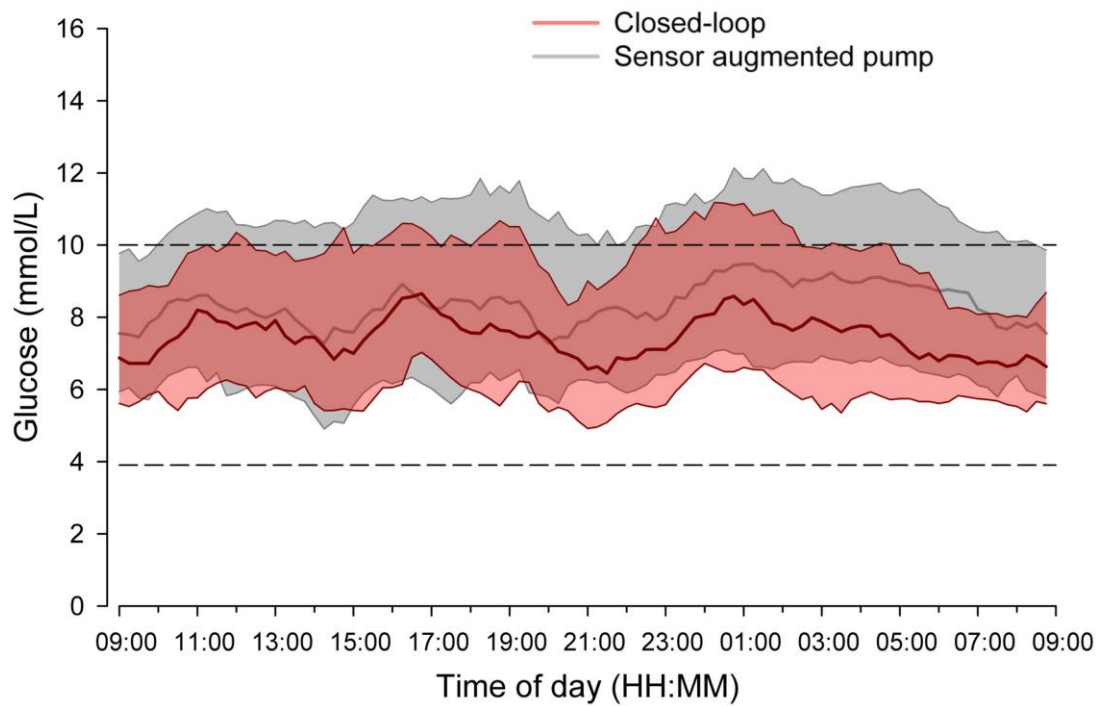
Data shown are mean ± SD or median (IQR) *Paired samples t tests or Wilcoxon signed rank test. AUC – area under the curve calculated per day, SD - Standard deviation, SAP - sensor augmented pump therapy.

[‡] Adjusted for CGM measurement error assuming a relative absolute deviation of 15%.

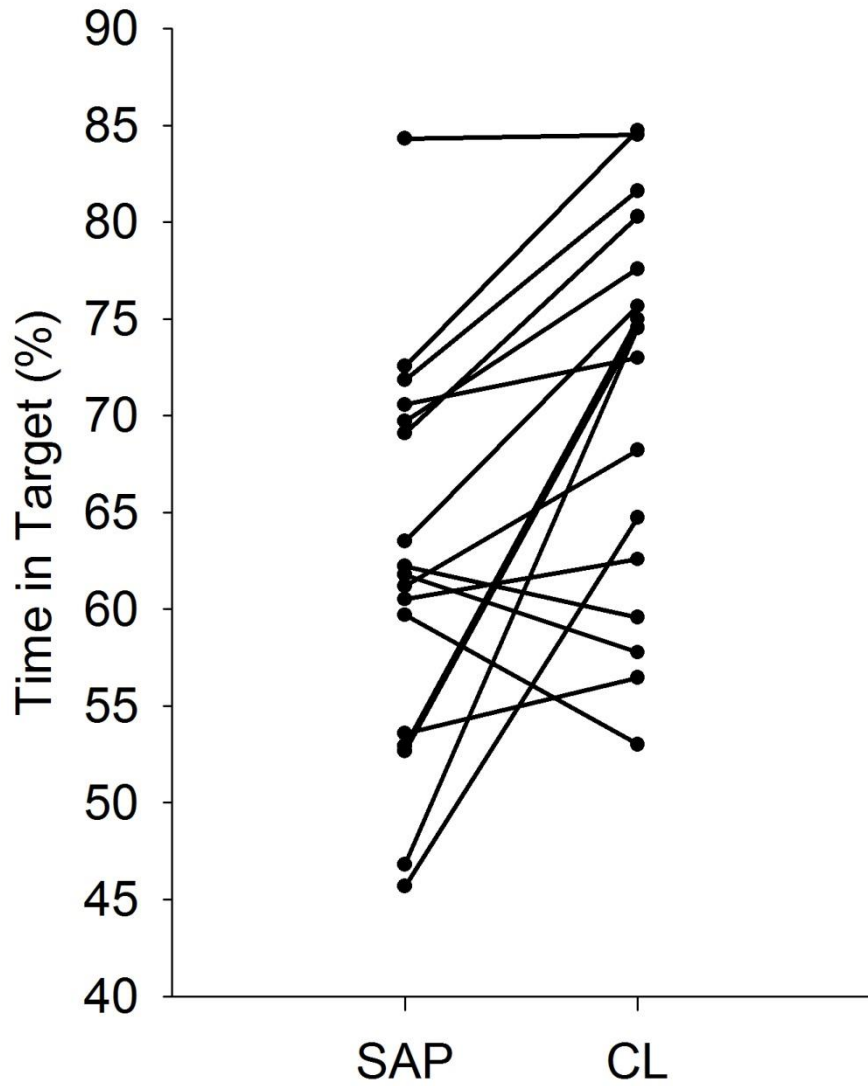
*Paired samples t-test or Wilcoxon signed rank test.

Figure Legends

1. Figure 1: 24 h Glucose profiles during home use of closed-loop and sensor augmented pump therapy. The target glucose range 3.9 to 10.0 mmol/l is denoted by the dashed lines. Data shown are median (interquartile range).



2. Figure 2: Time spent in target glucose range 3.9 to 10.0 mmol/l by participants (N=17) at home. Fourteen (82%) participants showed increased time in target range during closed-loop compared to sensor augmented pump therapy



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